any conclusions, but taken in connection with cases reported in the literature they are suggestive: (1) Jaundice occurring in the course of chronic tuberculosis is probably due to some form of tuberculosis of the liver, either extrahepatic or intrahepatic. (2) The grade of the jaundice is helpful in surmising the pathological condition, intense jaundice being probably due either to pressure of tuberculous glands on the extrahepatic ducts or to some form of the solitary tubercles of the liver; milder forms being produced by a miliary tuberculosis of the liver.

REFERENCES.

1. Rolleston, H. D. Diseases of Liver, Gall-bladder, and Bile Ducts, 1905.
2. Florand, M. La Semaine Médicale, 1899, p. 20.
3. Hodenpyl. Medical Record, 1898.
4. Knight. Quar. Med. Jour., Sheffield, July, 1895.
5. Köster, A. Centralbl. f. inn. Med., 1896, S. 213.
6. Arnold. Quoted from Ullom.
7. Rosenberger. Trans. Path. Soc. Phila., ix, 1906.
8. Simmond. Deutch. Arch. f. klin. Med., 1880, Band xxviii, 450.
9. Ullom. Proceedings of the Sixth International Congress on Tuberculosis, vol. I, Part I, 363.
10. Hale White, W. Common Affections of the Liver, 1908.
11. Bristowe, J. S. Transactions Path. Soc., London, ix, 241
12. Thayer. Johns Hopkins Hos. Bull., May, 1911.
13. Warthin. International clinics, vol. I, 21st series, 1911.
14. Mayo-Robson. Clin. Soc. Trans., London. 1895, xxviii, 83
15. Maylard, A. E. Abdominal Tuberculosis.
16. Wethered, F. J. Trans. Path. Soc., London, xl, 139.
17. Graham, J. E. American System of Practical Medicine, vol. III.
18. Murchison. Diseases of the liver, 3d edition, p. 279.

HYALINE DEGENERATION OF THE ISLANDS OF LANGERHANS IN NON-DIABETIC CONDITIONS.

By Russell L. Cecil, M.D.,

ASSISTANT PHYSICIAN TO THE PRESBYTERIAN HOSPITAL; INSTRUCTOR IN CLINICAL MEDICINE IN THE COLUMBIA UNIVERSITY MEDICAL SCHOOL, NEW YORK.

(From the Pathological Laboratory and the Medical Services of the Presbyterian Hospital, Columbia University, New York.)

Hyaline degeneration of the islands of Langerhans was first described in 1900 by Opie,[1] who noted its association with diabetes mellitus. Since then numerous observers have encountered hyaline islands in diabetes, and the condition is now recognized as a common finding in this disease.

In a series of 90 cases of diabetes which I[2] studied in 1909, sclerosis of the islands was noted in 60, and hyaline degeneration in 30 per cent. of the cases. Although hyaline change in the islands is so frequently encountered in the diabetic pancreas, its occurrence in the non-diabetic pancreas is rare—so rare, indeed, that the lesion is generally considered characteristic of diabetes. I have been able to find only five references to such exceptional cases in the literature.

---

[1] Jour. Exp. Med., 1900 to 1901, v, 397, 527.

[2] Cecil, Jour. Exp. Med., 1909, 266; 1911, xiv, 500.

The first case of hyaline degeneration of the islands without diabetes was reported by Ohlmacher[3] in 1904. The case was that of an man, aged seventy-two years, the immediate cause of whose death was mastoiditis, with thrombosis of the lateral sinus. At autopsy there was cirrhosis of the liver, chronic interstitial pancreatitis, arteriosclerotic atrophy of the kidneys, and general arteriosclerosis.

Fully four-fifths of the islands of Langerhans showed hyaline degeneration, while many of the surviving ones were hypertrophied. This patient had been under observation for nine months previous to his death, and at no time had he shown any symptoms of diabetes.

Whipple,[4] in 1907, in a study of pancreatitis and focal necroses, refers very briefly to two cases of hyaline degeneration of the islands that he observed in which there had been no evidence of diabetes. The first case was a colored man, aged twenty-three years, who died of tetanus. The anatomical diagnosis was appendectomy, general peritonitis, lobar pneumonia, focal necroses of the liver, cardiac hypertrophy, chronic gastritis, and chronic interstitial pancreatitis. The pancreas showed in addition to chronic inflammatory changes, hyaline degeneration of the islands of Langerhans.

Through the kindness of Dr. Whipple, I have been able to include the second of his cases in the present series. It will be described in detail farther on.

Saltykow,[5] in 1909, noted well-marked hyaline degeneration of some of the islands in the pancreas of a man, aged eighty-eight years, with advanced arteriosclerosis. There were also a number of necrotic foci in the pancreas (fat necroses?). At no time had he shown symptoms of diabetes.

Herxheimer[6] refers to a case of cirrhosis of the liver in which the pancreas was sclerotic and showed in addition a number of hyaline islands. At the time of the patient's death there was no diabetes, but on looking up his past history it was found that diabetes had existed before the onset of cirrhosis of the liver.

Milne and Peters,[7] in 1912, remarked that they had encountered hyaline degeneration of the islands in non-diabetic conditions, but beyond that statement proceeded no further in the matter.

---

[3] Amer. Jour. Med. Sci., 1904, cxxviii, 287.

[4] Bull. Johns Hopkins Hospital, 1907, xviii, 391.

[5] Korrespondensbl. f. Schweiz Aerzte, 1909, xxxix, 625.

[6] Verhandl. d. deutsch. path. Gesellsch., 1909, p. 276.

[7] Jour. Med. Research, 1912, xxvi, 405.

Of the 6 cases reported in this paper, 4 came from the clinics of the Presbyterian Hospital, 1 from the pathological department of the New York Hospital, and 1 from the pathological department of the Johns Hopkins Hospital. Synopses of these cases will be found at the end of the paper. A comparative study of these cases might be profitable as a means of approaching the problems of the pathogenesis of diabetes, particularly as regards the part played by the islands of Langerhans. In order to facilitate this comparison, I have prepared a table in which are catalogued the more important clinical and pathological data from the six cases.

TABLE OF CASES.

Case.	Age.	Sex.	Cause of death.	Pancreas.	Liver.	Kidneys.	Cardiovascular system.
I L. M.	60	M.	Epithelioma of inferior maxilla.	Chronic interstitial pancreatitis. Many fibrous and hyaline islands. Arterioles thickened.	Moderate cirrhosis.	Fibrous and hyaline glomeruli. Arterioles thickened and hyaline.	General arteriosclerosis. Chronic interstitial myocarditis.
II C. H. B.	43	M.	Cirrhosis of liver.	Slight chronic interstitial pancreatitis. Fibrous and hyaline islands. Arterioles thickened.	Advanced cirrhosis.	Fibrous and hyaline glomeruli. Arterioles slightly thickened.	General arteriosclerosis. Chronic endocarditis.
III M. M.	50	F.	Acute pericarditis.	Fat necroses. Moderate interstitial sclerosis and adiposis. Many hyaline islands. Arterioles thickened.	Fatty infiltration.	Chronic interstitial nephritis. Fibrous and hyaline glomeruli. Arterioles thickened.	General arteriosclerosis. Chronic endocarditis. Chronic myocarditis. Cardiac hypertrophy.
IV F. W.	42	M.	Typhoid fever.	Some sclerosis. Considearble adiposis. Many hyaline islands, a few hypertrophied. Arterioles thickened.	Focal necroses. Cloudy swelling.	Numerous hyaline glomeruli. Cloudy swelling. Arterioles thickened.	Arteriosclerosis.
V D. H.	37	M.	Endothelioma (?) (left orbit).	Metastases. Slight sclerosis. Many islands hyaline; some hypertrophied. Arterioles slighty thickened.	Metastatic nodules.	A few hyaline glomeruli. Compression atrophy about metastases. Glomerular capillaries thickened.	Slight atheroma of aorta.
VI H. T.	49	F.	Cardio-renal disease.	Considerable interstitial sclerosis. Many hyaline islands. Arterioles thickened.	Congestion.	Chronic diffuse nephritis. Many fibrous and hyaline glomeruli. Arterioles thickened.	Cardiac hypertrophy and dilatation Diffuse myocarditis and fatty degeneration. Verrucous endocarditis. Arteriosclerosis.

In the first place it will be noticed that the condition occurred in middle-aged or elderly people, in this respect resembling diabetes. Four of the six cases were in men. None of the cases gave any history of diabetes; in none of them did the urine show glucose while under observation; in none of the cases was there any history or evidence of lues; in three there was a history of excessive indulgence in alcohol.

The immediate cause of death was an acute infection in 2 cases, a malignant neoplasm in 2, chronic nephritis in 1, and cirrhosis of the liver in 1 case.

The most interesting points from comparison bore on the pathological changes noted in the various organs. In the first place there was noted in every case an interstitial pancreatitis of the type usually seen in diabetes, and more or less thickening of the pancreatic arterioles. The new-formed connective tissue was irregularly distributed, the pancreas appearing normal in some places, while in others there was definite interacinar sclerosis. In Cases IV and V the sclerosis was slight and visible at only a few points. The islands were in no instance entirely destroyed; on the contrary, perfectly normal islands could always be found. A certain number, however, showed more or less extensive hyaline degeneration, which apparently originated about the thickened insular capillaries. The hyaline changes were associated in most instances with a certain amount of insular sclerosis. So far as the pancreas was concerned then it would have been impossible to distinguish the lesions from those observed so frequently in diabetes.

In two of my cases there was a well-marked cirrhosis of the liver, a condition which also occurred in the cases of Ohlmacher and of Herxheimer. In Herxheimer's case there had previously been some glycosuria, but at the time of the hepatic cirrhosis the glycosuria had entirely disappeared. Herxheimer suggested that the disappearance of the glucose might have been dependent in some way on the development of the hepatic cirrhosis.

The condition of the kidneys in my series is particularly interesting. In every case there was a definite fibrosis and hyaline degeneration of some of the glomeruli, associated with sclerosis of the renal arterioles and glomerular capillaries. The lesions were not advanced (except in two of the cases) and were confined for the most part to the glomeruli. The frequent association of chronic nephritis with diabetes has been often observed, especially in those cases where arteriosclerosis is present. Indeed, it is the arteriosclerotic type of nephritis that is usually seen in this connection.

In view then of the frequent association of diabetes and arteriosclerosis it is significant that in the present six cases of pancreatic and insular lesions, arteriosclerosis was noted in all, in four instances being associated with cardiac lesions. In Cases IV and V, the vascular changes were slight and largely confined to the smaller vessels of the pancreas and kidney, while in the remaining cases the process was more generally distributed.

Discussion. What bearing has the occurrence of hyaline degeneration of the islands of Langerhans in non-diabetic conditions on the island theory of diabetes? For my own part I cannot see that it vitiates that theory in any way. Certainly, no one would think of doubting the effect of sclerosis and hyaline degeneration of the glomeruli on renal efficiency, because one sometimes sees hyaline glomeruli in a kidney which during life has manifested no signs of disease.

Two explanations are open to us. In the first place it is quite possible that the destructive process in the islands has not advanced far enough to produce diabetes. The number of islands varies greatly in different individuals. Those with a large number could probably stand considerable destruction of island tissue without showing symptoms, for Nature has doubtless provided many more islands than are actually needed for efficient carbohydrate metabolism. Organs are constantly being encountered at the postmortem which, while diseased, had not advanced as yet to the symptom-producing stage; for example, cirrhosis of the liver without jaundice or ascites, shrunken kidneys without albuminuria, endocarditis without incompetence, etc. So it may be assumed that destruction of the islands must progress to a certain point before glycosuria appears.

The other explanation is that the patient had diabetes at one time, but that other organs have vicariously assumed the pancreatic function with so much success that they have completely supplied the deficiency in that organ. Personally, I should rather favor the former hypothesis for the reason that in no one of the six cases had the hyaline degeneration involved all the islands. Moreover, one would expect to see more evidence of regeneration or hypertrophy of the islands if at any time there had been much demand for an increase in their functional activity. In a previous paper I[8] have shown that in a considerable proportion of diabetic pancreases there has occurred more or less regeneration and hypertrophy of the islands, the new-formed islands budding off from the ducts after the manner of those observed in the fetal pancreas. The absence of this phenomenon may be taken to suggest that in the six cases which have been reported diabetes had at no time existed.

An interesting phenomenon observed in this study is the coincidence of hyaline degeneration of the islands and of the glomeruli. In the kidney, fibrous and hyaline glomeruli are very common, and have usually been interpreted as the sequel of renal arteriosclerosis. Possibly the same explanation holds for hyaline changes in the islands of Langerhans. It is conceivable that in both instances the vascular changes have involved particularly the capillaries supplying these structures, with the result that sclerosis and hyaline degeneration have ensued. And just as arteriosclerosis is now recognized as the usual precursor of the so-called "contracted kidney," with its interstitial fibrosis and glomerular lesions, so pancreatic diabetes may eventually be shown to depend upon a preëxistent arteriosclerosis, which, interfering with the pancreatic vascular supply has induced an interstitial pancreatitis and degenerative changes in the islands of Langerhans. I would also put forward the suggestion that the hyperglycemia which has been observed in cases of arteriosclerosis, with high tension, might be explained by the same theory as an incipient disturbance of the internal secretion of the pancreas due to pancreatic arteriosclerosis.

---

[8] Loc. cit.

SUMMARY. Six cases of hyaline degeneration of the islands of Langerhans, in which there was no evidence of diabetes have been reported. All occurred in subjects aged over thirty-seven years. In addition to the hyaline changes there were found in every case more or less sclerosis of the insular capillaries, and a chronic interacinar pancreatitis of the type usually encountered in diabetes mellitus.

The explanation of this phenomenon, which has seemed most likely is that hyaline degeneration of the islands, may occur up to a certain point without producing diabetes. When a number of islands, sufficient to interfere with carbohydrate metabolism, have been involved, diabetes ensues.

The hyaline changes in the islands of Langerhans have been associated in every case with hyaline degeneration of the renal glomeruli. The lesions in both instances are possibly referable to sclerosis of the smaller vessels supplying these structures.

SYNOPSES OF CASES.

CASE I.—L. M., male, aged sixty years. Admitted to Dr. Blake's service at the Presbyterian Hospital with epithelioma of lower jaw. Urine free from glucose. Patient died following partial resection of lower jaw.

Autopsy 8081. Anatomical diagnosis: Amputation of the left inferior maxilla (epithelioma), acute bronchopneumonia, general arteriosclerosis, chronic interstitial myocarditis, cirrhosis of the liver, cholelithiasis, chronic interstitial pancreatitis, chronic diffuse nephritis.

Pancreas: Small and firm. On section it contained considerable fatty tissue. Microscopically there was an irregularly distributed sclerosis and fatty infiltration. Arteries were thickened and hyaline. The epithelium lining the larger ducts had undergone adenomatous proliferation. Islands were numerous, some appearing normal, others sclerotic, still others, perhaps 25 per cent., showed more or less hyaline degeneration.

Liver: Weight, 1210 gm. Surface smooth, but on section, lobules were small and distinct. Microscopically there was considerable increase of the interlobular connective tissue and infiltration of lymphoid cells. Hepatic arteries were thickened and hyaline.

Gall-bladder: Contained a large stone.

Kidneys: Weight (together) 290 gm. Macroscopically they showed nothing of interest. Microscopically the glomeruli showed fibrous and hyaline changes. There was considerable granular degeneration and disintegration of the tubular epithelium. Arterioles were thickened and hyaline. The thyroid and suprarenals were normal.

Case II.—C. H. B., male, aged forty-three years; moderately alcoholic. Admitted to the medical service of the Presbyterian Hospital, with jaundice and continuous fever. After several weeks of observation he was transferred to the surgical side for exploratory laparotomy. At operation, cirrhosis of liver and ascites were found. Patient died several days after the operation. Repeated examinations of the urine were negative.

Autopsy 7781. Anatomical diagnosis: Cirrhosis of the liver, chronic endocarditis, chronic glomerular nephritis, chronic interstitial pancreatitis, general arteriosclerosis, chronic interstitial splenitis, acute bronchopneumonia.

Pancreas: In the gross was apparently normal. Microscopically there were patches of sclerosis here and there. Small arteries were thickened and hyaline. Islands were sclerotic and in many cases hyaline. The stroma was infiltrated with lymphoid cells in places. Ducts were normal.

Liver: Weight, 1440 gm. Surface was markedly granular. On section the organ was tough and the cut surface was granular, the yellow elevated lobules being separated by pale gray tissue. Microscopically there was typical cirrhosis in the advanced stage, with extensive new formation of small ducts and dense infiltration of stroma, with lymphoid cells. Hepatic arteries thickened and hyaline. Portal capillaries were dilated.

Kidney: Some of the glomeruli had been converted into hyaline or fibrous tufts. There was slight thickening of some of the vessels. Tubular epithelium was broken down in places.

Case III.—M. M., female, aged fifty years. Admitted to the second medical service of the Presbyterian Hospital during an exacerbation of arthritis deformans. Urine showed faint trace of albumin and casts, but no glucose at any time during her stay of one year in the hospital. The patient died of acute pericarditis.

Autopsy 7981. Anatomical diagnosis: Acute serofibrinous pericarditis, chronic endocarditis (mitral and aortic valves), hypertrophy of heart, chronic interstitial myocarditis, chronic interstital nephritis, fatty infiltration of the liver, chronic interstitial pancreatitis, fat necroses in the pancreas, general arteriosclerosis, hypertrophic arthritis deformans, etc.

Pancreas: Firm and of good size. Small yellowish areas scattered over the surface. Islands visible. Ducts normal. Microscopically there was some increase of the stroma in places and considerable adipose tissue was found between the lobules. Here and there were collections of lymphoid cells, and at some points in the fatty tissue there were seen small foci of necrosis, surrounded by leukocytes. The islands were numerous and rather large. About two-thirds of them showed definite hyaline changes, the process being advanced in some cases. Small arteries were thickened and hyaline.

Liver: Centres of lobules congested. Hepatic arteries showed considerable thickening and hyaline degeneration.

Kidney: Well-marked increase of stroma in the cortex, especially about the glomeruli; the latter showed fibrous and hyaline changes, moderate infiltration of stroma, with lymphoid cells. Small arteries were thickened and hyaline. The cells of the convoluted tubules were in places granular and vacuolated.

Thyroid: Slight increase of stroma. Suprarenals and hypophysis were normal.

Case IV.—F. W., male, aged forty-two years. Admitted to the second medical service at the Presbyterian Hospital for typhoid fever. Died ten days after admission, with bronchopneumonia. Urine was negative.

Autopsy 8197. Anatomical diagnosis: Typhoid fever, typhoid ulcers of the ileum and ascending colon, acute splenic tumor, focal necroses of the liver, cloudy swelling of the viscera, fragmentation of the heart muscle, bronchopneumonia, acute fibrinous pleuritis, chronic interstitial pancreatitis, slight arteriosclerosis. Atheroma of aorta.

Pancreas: In the gross appeared normal. Microscopically there was considerable fatty tissue between the lobules. Parenchyma were well-preserved. There was some increase of the interstitial tissue in places. The islands were not noticeably increased in number. Some of them were normal, but at least half of them showed more or less extensive hyaline degeneration. In some there had been almost complete destruction of the island cells. A few islands were hypertrophied. Arterioles were thickened.

Liver: Swollen and cloudy. Gall-bladder and ducts were normal. Microscopically there was considerable postmortem change. Vacuoles were numerous. There was well-marked focal necrosis, generally about the central veins.

Kidneys: Measured 11 x 5.5 x 3 cm. Fibrous capsule slightly adherent. Surface and cut surface appeared normal. Microscopically there was some granular degeneration of the tubular epithelium (probably postmortem); hyaline glomeruli were numerous. Arterioles were thickened.

Case V.—H., male, aged thirty-seven years. Admitted to New York Hospital complaining of pain in abdomen and diarrhea.

Physical examination (on admission) showed the liver enlarged, edge 9½ inches below costal margin, firm but not tender. Patient's head was considerably enlarged, and there was marked bulging of the left eye. Patient was in the hospital about a year. Repeated examinations of the urine showed a trace of albumin and hyaline and granular casts, but no glucose.

Clinical Diagnosis: New growth of liver.

Autopsy 4465. Anatomical diagnosis: Tumor (endothelioma?) of the left orbit; metastases in liver, kidneys, pancreas, lungs, heart, bronchial, and retroperitoneal lymph glands; abscess of the lung, acromegaly, arteriosclerosis.

Tumor of the Orbit: Right orbit contained a tumor the size of a bantam's egg, situated between the base of the orbit and the optic nerve, easily removed, adherent to sheath of optic nerve; consistence firm; cut surface was grayish pink and granular. Eyeball pushed forward; base of orbit was slightly eroded.

Microscopic Examination: The tumor was composed of alveoli filled with small, flattened endothelial cells, with large chromatic nuclei and small amount of pale cytoplasm. In some places the connective tissue was scanty and the alveoli large; in others the stroma was very abundant and richly vascularized and infiltrated with cords of tumor cells.

Liver: Greatly enlarged, and contained many small tumor nodules.

Microscopic Examination: Sections through tumor nodules differed in no way from those of original tumor.

Pancreas: There were numerous small tumor nodules in the pancreas similar to those in the liver. The tail of the pancreas, though free from tumor, appeared rather firm. Ducts were patent. Microscopically there was a slight increase of connective tissue in some places about the ducts, elsewhere the stroma as well as the glandular acini appeared normal. At least three-quarters of the islands of Langerhans showed hyaline degeneration, which in some cases was advanced. Islands were hypertrophied. Arterioles were slightly thickened. Larger ducts showed adenomatous hypertrophy of lining epithelium. Metastases composed of tumor cells, similar to those in liver. In places they completely surrounded the islands, which may have been normal or hyaline.

Kidneys: Weight (together), fifteen ounces. Upon stripping off the capsule small tumors were seen projecting above the surface, which was otherwise smooth. On section the markings were indistinct. Tumor nodules were scattered through the cortex; pyramids appeared normal. Microscopically there was granular degeneration of the tubular epithelium; a few of the glomeruli showed hyaline degeneration. Glomerular capillaries thickened. Tumor nodules were similar to those described above.

Hypophysis: Enlarged, size of small walnut, and soft.

Microscopic Examinations: Section showed a richly vascularized connective tissue supporting a large number of solid glandular tubules containing rounded or flattened epithelial cells. Occasional hollow tubules lined with low cuboidal cells and filled with colloid material were observed.

Case VI.—H. T., female, aged forty-nine years; colored. Admitted to the Johns Hopkins Hospital for chronic nephritis.

Autopsy 2895. Anatomical diagnosis: Chronic diffuse nephritis (large white kidney), cardiac hypertrophy and dilatation, diffuse myocarditis and fatty degeneration; verrucous tricuspid, and aortic endocarditis, hemorrhagic gastritis, catarrhal enteritis, general anasarca, edema and atelectasis of lungs, myomas of uterus, pelvic peritonitis, general arteriosclerosis, chronic pancreatitis, colloid goitre, obesity.

Pancreas: Normal in size and consistence. Cut showed distortion of lobules. Ducts were dilated and a little thickened.

Microscopic Examination: There was considerable increase of the interstitial tissue, with atrophy of many of the acini. Islands were fairly numerous. Insular capillaries were thickened. A considerable number of the islands had undergone hyaline degeneration, and in some cases to an extreme degree.

Kidney: Microscopically there was extensive replacement of the cortex by fibrous tissue, with considerable granular degeneration and desquamation of the tubular epithelium. There were many hyaline and fibrous glomeruli. Well-marked thickening of the renal arterioles was observed.

Liver: Microscopically there was congestion of the lobules about the central veins, with some compression atrophy of the cells.

Note.—I am indebted to Dr. George H. Whipple, of the Johns Hopkins Hospital, and to Dr. William J. Elser, of the New York Hospital, for pathological material and for permission to report two of the cases included in this study.

ALCOHOLISM AND EPILEPSY, ALSO SO-CALLED ACUTE ALCOHOLIC EPILEPSY.[1]

By N. S. Yawger, M.D.,

EXAMINING PHYSICIAN TO THE PENNSYLVANIA EPILEPTIC HOSPITAL AND COLONY FARM, PHILADELPHIA.

(From the Department of Neurology in the University of Pennsylvania.)

The craving for alcohol and alkaloids or substances that are similar to these in their action is so universal as to appear almost

[1] Read before the Chester County Medical Society at Embreeville, Pa., July 8, 1913.